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(FILE 'HOME' ENTERED AT 10:14:23 ON 21 AUG 2001)

FILE 'CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 10:14:38 ON 21 AUG 2001

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L1       152118 S (TREATMENT OR THERAPY) AND (NEUROLOGICAL DISEASE OR
ALZHEIMER
L2        15855 S L1 AND (DIFFICULT? OR CHALLENG? OR PROBLEM? OR COMPLEX? OR
CO
L3          410 S L2 AND (CELL REPLACEMENT OR TRANSPLANT OR GRAFT)
L4          459 S L2 AND (CELL REPLACEMENT OR TRANSPLANT OR GRAFT OR EX VIVO)
L5         9399 S L1 AND (DIFFICULT? OR CHALLENG? OR PROBLEM?)
L6         9399 S L5 AND (DIFFICULT? OR CHALLENG? OR PROBLEM?)
L7          278 S L5 AND (CELL REPLACEMENT OR TRANSPLANT OR GRAFT OR EX VIVO)
L8           38 S L7 AND REVIEW
L9           33 DUP REMOVE L8 (5 DUPLICATES REMOVED)
L10           0 S L4 AND (SUSTAINED EXPRESSION OR MAINTAIN? EXPRESSION)
L11          77 S L4 AND (SUSTAINED EXPRESSION OR MAINTAIN? EXPRESSION OR EXPR
L12           2 S L11 AND (SUSTAIN OR MAINTAIN)
L13           2 DUP REMOVE L12 (0 DUPLICATES REMOVED)
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(FILE 'HOME' ENTERED AT 10:14:23 ON 21 AUG 2001)

FILE 'CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 10:14:38 ON 21 AUG 2001

L1	152118	S (TREATMENT OR THERAPY) AND (NEUROLOGICAL DISEASE OR ALZHEIMER
L2	15855	S L1 AND (DIFFICULT? OR CHALLENG? OR PROBLEM? OR COMPLEX? OR CO
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L4	459	S L2 AND (CELL REPLACEMENT OR TRANSPLANT OR GRAFT OR EX VIVO)
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L6	9399	S L5 AND (DIFFICULT? OR CHALLENG? OR PROBLEM?)
L7	278	S L5 AND (CELL REPLACEMENT OR TRANSPLANT OR GRAFT OR EX VIVO)
L8	38	S L7 AND REVIEW
L9	33	DUP REMOVE L8 (5 DUPLICATES REMOVED)
L10	0	S L4 AND (SUSTAINED EXPRESSION OR MAINTAIN? EXPRESSION)
L11	77	S L4 AND (SUSTAINED EXPRESSION OR MAINTAIN? EXPRESSION OR EXPR
L12	2	S L11 AND (SUSTAIN OR MAINTAIN)
L13	2	DUP REMOVE L12 (0 DUPLICATES REMOVED)
L14	53	S L4 AND GENE THERAPY
L15	6	S L14 AND REVIEW
L16	42	DUP REMOVE L14 (11 DUPLICATES REMOVED)
L17	6	DUP REMOVE L15 (0 DUPLICATES REMOVED)

L9 ANSWER 2 OF 33 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:108147 SCISEARCH
THE GENUINE ARTICLE: 395RD
TITLE: Transplantation and gene **therapy**: Combined approaches for repair of spinal cord injury
AUTHOR: Murray M (Reprint); Fischer T
CORPORATE SOURCE: Med Coll Penn & Hahnemann Univ, Dept Neurobiol & Anat, Philadelphia, PA 19129 USA
COUNTRY OF AUTHOR: USA
SOURCE: NEUROSCIENTIST, (FEB 2001) Vol. 7, No. 1, pp. 28-41. Publisher: SAGE PUBLICATIONS INC, 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA.
ISSN: 1073-8584.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 70

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Motor and sensory functions are lost after spinal cord injury because neurons die or atrophy and axons fail to regenerate. Until fairly recently, it was believed that damaged neurons could not be replaced and injured axons could not regenerate, and, therefore, functions dependent on injured neurons could not be recovered, We now know that damaged neurons can be rescued by providing therapeutic factors or replaced by grafting. In addition, the adult CNS contains a population of precursor cells with a potential to generate new neural cells, whose numbers and composition can be modified by extrinsic factors. The pioneering studies of Aguayo demonstrated that CNS axons could regenerate in the right environment. Subsequent studies have revealed the identity of some of the inhibitory molecules in myelin and scar tissue, and we now have a better understanding of how the CNS environment can be modified to become more permissive to regeneration. Axons that regenerate must find an appropriate target, but it may not be essential to reestablish the precise topography for some functions to be restored. There are now new and promising strategies for delivery of therapeutic genes to protect neurons and to stimulate regeneration. The ability to engineer cells by gene **therapy** combines the therapeutic values of cell transplantation and gene delivery. These remarkable developments from many disciplines have generated a new level of optimism in the search for a cure for CNS injury and in particular spinal cord injury. In this **review**, the authors summarize recent progress in these strategies and some of the **challenges** that remain in elucidating the most efficacious protocols for rescuing injured neurons, encouraging regeneration of their axons, and promoting recovery of function.

L9 ANSWER 5 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:812241 CAPLUS
DOCUMENT NUMBER: 134:40213
TITLE: Neurons from stem cells: implications for understanding **nervous system** development and repair
AUTHOR(S): Mansergh, Fiona C.; Wride, Michael A.; Rancourt, Derrick E.
CORPORATE SOURCE: Departments of Oncology and Biochemistry & Molecular Biology, The University of Calgary, Calgary, AB, T2N

1N4, Can.
SOURCE: Biochem. Cell Biol. (2000), 78, 613-628
CODEN: BCBIEQ; ISSN: 0829-8211
PUBLISHER: National Research Council of Canada
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** with 148 refs. Neurodegenerative diseases cost the economies of the developed world billions of dollars per annum. Given aging population profiles and the increasing extent of this **problem**, there has been a surge of interest in neural stem cells and in neural differentiation protocols that yield neural cells for therapeutic transplantation. Due to the oncogenic potential of stem cells, a better characterization of neural differentiation, including the identification of new neurotrophic factors, is required. Stem cell cultures undergoing synchronous in vitro neural differentiation provide a valuable resource for gene discovery. Novel tools such as microarrays promise to yield information regarding gene expression in stem cells. With the completion of the yeast, C. elegans, Drosophila, human, and mouse genome projects, the functional characterization of genes using genetic and bioinformatic tools will aid in the identification of important regulators of neural differentiation.

REFERENCE COUNT: 143
REFERENCE(S): (1) Arsenijevic, Y; J Neurosci 1998, V18, P2118 CAPLUS
(2) Bain, G; Biochem Biophys Res Commun 1996, V223, P691 CAPLUS
(3) Bain, G; Bioessays 1994, V16, P343 CAPLUS
(4) Bain, G; Dev Biol 1995, V168, P342 CAPLUS
(6) Bain, G; Perspect Dev Neurobiol 1998, V5, P175 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 6 OF 33 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:692071 SCISEARCH
THE GENUINE ARTICLE: 351YR
TITLE: Progress in spinal cord research - A refined strategy for the International Spinal Research Trust
AUTHOR: Ramer M S (Reprint); Harper G P; Bradbury E J
CORPORATE SOURCE: GUYS KINGS & ST THOMAS SCH BIOMED SCI, NEUROSCI RES CTR, SHERRINGTON BLDG, ST THOMAS CAMPUS, LONDON SE1 7EH, ENGLAND (Reprint); SMITHKLINE BEECHAM PHARMACEUT, HARLOW CM19 5AD, ESSEX, ENGLAND
COUNTRY OF AUTHOR: ENGLAND
SOURCE: SPINAL CORD, (AUG 2000) Vol. 38, No. 8, pp. 449-472. Publisher: NATURE PUBLISHING GROUP, HOUNDMILLS, BASINGSTOKE RG21 6XS, HAMPSHIRE, ENGLAND. ISSN: 1362-4393.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: CLIN
LANGUAGE: English
REFERENCE COUNT: 193

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Achieving regeneration in the central **nervous system** represents one of the greatest intellectual and practical **challenges** in neurobiology, and yet it is an absolute requirement if spinal cord injury patients are to have any hope of recovery. The mission of the International Spinal Research Trust (ISRT), established in 1980, is to raise money specifically for spinal research, with a view to ending the permanence of paralysis caused by spinal cord injury. This **review** summarises some of the major steps forward made in recent years in understanding the mechanisms involved in spinal cord injury and where these discoveries fit in with the ISRT's overall objectives. We **review** approaches aimed at (1) preventing immediate adverse reactions to injury such as neuronal death and scar formation; (2)

minimising inhibitory properties of the CNS environment and maximising the growth potential of damaged neurons; (3) understanding axonal guidance systems that will be required for directed outgrowth and functional reconnection; and (4) optimising the function of surviving systems. We also discuss 'infrastructural' prerequisites for applying knowledge gained through spinal research to the clinical condition, including basic scientific issues such as developing representative animal models of spinal cord injury and sensitive quantitative methods for assessing growth and functional restoration. In addition, we point out the importance of communication. The need to share knowledge between research groups is vital for advancing our understanding of injury and repair mechanisms. Equally important is the need for communication between basic scientists and clinicians which will be essential for what is the ultimate goal of the ISRT, the development of relevant **treatment** strategies that will prove beneficial to the spinal injured patient.

L9 ANSWER 9 OF 33 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 2000:399539 BIOSIS
DOCUMENT NUMBER: PREV200000399539
TITLE: Neural tissue xenografting.
AUTHOR(S): Larsson, L. C. (1); Widner, H.
CORPORATE SOURCE: (1) Section for Neuronal Survival, Wallenberg Neuroscience Center, Solvegatan 17, S-223 62, Lund Sweden
SOURCE: Scandinavian Journal of Immunology, (September, 2000) Vol. 52, No. 3, pp. 249-256. print.
ISSN: 0300-9475.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Neural transplantation may become an important **treatment** alternative for focal brain disorders. To date, the most successful **grafts** have been obtained in patients with Parkinson's disease. Completely normalized dopamine production and reduction of Parkinsonian symptoms have been demonstrated 10 years after grafting. However, the allogeneic donor tissue has to be obtained from induced abortions, and there are logistical **difficulties**, risks of infection, and ethical constraints limiting a wider clinical use. Xenografting is an alternative that could bridge these limitations if immunological rejection could be prevented. Pig embryonic neural tissue has been grafted to patients with Parkinson's disease, but no functional benefits have clinically been proven so far. The immune reactions to neural xenografts were incompletely characterized at the time of these early clinical trials, and it is likely that the **treatments** used were insufficient and that the **grafts** were rejected. In this article we will **review** new experiments addressing the immune responses against porcine neural tissue grafted to the adult brain, including the role of antibodies, complement, natural killer (NK) cells, lymphocytes, as well as the effects of immunosuppressive drugs and donor tissue modifications.

L9 ANSWER 11 OF 33 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
ACCESSION NUMBER: 2000:288815 BIOSIS
DOCUMENT NUMBER: PREV200000288815
TITLE: Neural stem cells: From cell biology to **cell replacement**.
AUTHOR(S): Armstrong, Richard J. E.; Svendsen, Clive N.
SOURCE: Cell Transplantation, (March April, 2000) Vol. 9, No. 2, pp. 139-152. print..
ISSN: 0963-6897.
DOCUMENT TYPE: General Review

LANGUAGE: English
SUMMARY LANGUAGE: English

AB A large number of crippling neurological conditions result from the loss of certain cell populations from the **nervous system** through disease or injury, and these cells are not intrinsically replaced. Mounting evidence now suggests that replacement of depleted cell populations by transplantation may be of functional benefit in many such diseases. A diverse range of cell populations is vulnerable, and the loss of specific populations results in circumscribed deficits in different conditions. This diversity presents a considerable **challenge** if **cell replacement therapy** is to become widely applicable in the clinical domain, because each condition has specific requirements for the phenotype, developmental stage, and number of cells required. An ideal cell for universal application in **cell replacement therapy** would possess several key properties: it would be highly proliferative, allowing the **ex vivo** production of large numbers of cells from minimal donor material; it would also remain immature and phenotypically plastic such that it could differentiate into appropriate neural and glial cell types on, or prior to, transplantation. Critically, both proliferation and differentiation would be controllable. This **review** considers some of the evidence that stem cells exist in the central **nervous system** and that they may possess characteristics that make them ideal for broad application in **cell replacement therapy**.

L9 ANSWER 16 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:20171 CAPLUS
DOCUMENT NUMBER: 130:245945
TITLE: Neural stem cell lines for CNS repair
AUTHOR(S): Martinez-Serrano, Alberto; Snyder, Evan Y.
CORPORATE SOURCE: Center of Molecular Biology "Severo Ochoa,", Autonomous University of Madrid-CSIC, Madrid, Spain
SOURCE: CNS Regener. (1999), 203-250. Editor(s): Tuszynski, Mark H.; Kordower, Jeffrey H. Academic: San Diego, Calif.
CODEN: 67CYA3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A **review** with 112 refs. The establishment and use of stable, engraftable, clonal, multipotent neural stem cell lines have recently added an exciting new dimension to strategies for **cell replacement** and gene transfer to the diseased mammalian CNS. These neural stem cell clones can serve as convenient, well-controlled models for the in vivo study of CNS development and regeneration; can constitute readily available, well-characterized, safe sources of **graft** material for the replacement of multiple types of degenerated neural cells; and can provide excellent vehicles for the transfer of genes encoding diffusible and non-diffusible factors directly to the CNS. By exploiting their basic biol. properties, these cells are be able to bypass restrictions imposed by the blood-brain barrier to deliver therapeutic gene products in a sustained, direct, and perhaps regulated fashion throughout the CNS (either because they intrinsically produce these substances or because they have been genetically engineered **ex vivo** to do so). Furthermore, although they may disseminate these gene products throughout the brain, they nevertheless restrict that distribution to only the CNS. In addn., they may replace dysfunctional neural cells in both a site-specific and more global manner (circumventing the concern that in many alternative gene transfer techniques "new" genetic information is supplied to "old" neural circuits, many of which may have degenerated). Neural stem cell clones may be used for neurodegenerative conditions that occur both during development and in

the mature brain. In fact, they appear to be capable of altering their migration and differentiation in response to certain as yet unspecified signals elaborated during active neurodegeneration. Thus, these vehicles may overcome many of the limitations of viral and non-neural cellular vectors, as well as pharmacol. and genetic interventions. A growing body of evidence has, indeed, affirmed the efficacy of a neural stem cell-based strategy for the replacement of defective or absent genes and cells, and has suggested that re-population of the diseased or injured CNS with such cells may promote both anatomical and behavioral recovery in animal models of neurodegenerative conditions. These recent expts. with clones of rodent neural progenitor and stem cells are bringing us rapidly closer to the **challenge** of repairing the CNS in genuine clin. settings using similarly well-characterized, fully controlled, multifaceted cellular tools of human origin.

REFERENCE COUNT: 112

REFERENCE(S):
(1) Aboody-Guterman, K; Neuro Report 1997, V8(17), P3801 CAPLUS
(7) Bartlett, P; Proc Natl Acad Sci USA 1988, V85, P3255 CAPLUS
(9) Bencsics, C; J Neurosci 1996, V16, P4449 CAPLUS
(17) Cattaneo, E; Dev Brain Res 1994, V83, P197 CAPLUS
(19) Chen, K; J Neurosci 1995, V15, P2819 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 19 OF 33 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 4

ACCESSION NUMBER: 1999:508792 BIOSIS
DOCUMENT NUMBER: PREV199900508792
TITLE: Efficacy of grafted immortalized dopamine neurons in an animal model of Parkinsonism: A **review**.
AUTHOR(S): Prasad, Kedar N. (1); Clarkson, Edward D.; La Rosa, Francisco G. (1); Edwards-Prasad, Judith (1); Freed, Curt R.
CORPORATE SOURCE: (1) Cent. Vitamins Cancer Res., Univ. Colo. Health Sci. Center, Denver, CO 80262 USA
SOURCE: Molecular Genetics and Metabolism, (Sept., 1998) Vol. 65, No. 1, pp. 1-9.
ISSN: 1096-7192.
DOCUMENT TYPE: General Review
LANGUAGE: English

AB Dopamine (DA) deficiency is one of the primary lesions in the pathogenesis of Parkinson disease (PD). Because of long-term toxicity of L-DOPA **therapy**, the grafting of fetal mesencephalic tissue containing dopamine neurons or homogeneous populations of DA neurons into striatum appears to be rational. Fetal tissue **transplants** have many **problems** which include legal (in some countries), ethical, paucity of tissue availability, heterogenicity of cell populations, and the presence of antigen-presenting cells that are responsible for rejection of allogeneic **grafts**. In order to resolve the above **problems**, we have established immortalized DA neurons from fetal rat mesencephalon by inserting the large T-antigen (LTa) gene of the SV40 virus into the cells. A clone of DA neurons (IRB3AN27) was isolated, characterized, and tested in 6-hydroxydopamine (6-OHDA)-lesioned rats (a model of PD). These cells divided with a doubling time of about 26 h, expressed the LTa gene, and contained the tyrosine hydroxylase and dopamine transporter proteins and their respective mRNAs, which became elevated upon differentiation. These cells were nontumorigenic and nonimmunogenic and improved the symptoms of neurological deficits (methamphetamine-induced rotation) in 6-OHDA-lesioned rats. The differentiated DA neurons were more effective than undifferentiated ones. These studies suggest that immortalized DA neurons generated in vitro by

LTa gene insertion may be used in **transplant therapy** without fear of [redacted] formation or rejection.

L9 ANSWER 21 OF 33 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:724899 CAPLUS
DOCUMENT NUMBER: 128:73182
TITLE: Immortalized neural progenitor cells for CNS gene transfer and repair
AUTHOR(S): Martinez-Serrano, Alberto; Bjorklund, Anders
CORPORATE SOURCE: Center Biology 'Severo Ochoa', Autonomous University Madrid, Madrid, 28049, Spain
SOURCE: Trends Neurosci. (1997), 20(11), 530-538
CODEN: TNSCDR; ISSN: 0166-2236
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review** with 58 refs. Immortalized multipotent neural stem and progenitor cells have emerged as a highly convenient source of tissue for genetic manipulation and **ex vivo** gene transfer to the CNS. Recent studies show that these cells, which can be maintained and genetically transduced as cell lines in culture, can survive, integrate and differentiate into both neurons and glia after transplantation to the intact or damaged brain. Progenitors engineered to secrete trophic factors, or to produce neurotransmitter-related or metabolic enzymes can be made to repopulate diseased or injured brain areas, thus providing a new potential therapeutic tool for the blockade of neurodegenerative processes and reversal of behavioral deficits in aminal models of neurodegenerative diseases. With further tech. improvements, the use of immortalized neural progenitors may bring us closer to the **challenging** goal of targeted and effective CNS repair.

L9 ANSWER 23 OF 33 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 96:406740 SCISEARCH
THE GENUINE ARTICLE: BF47T
TITLE: THE **PROBLEMS** OF DELIVERING NEUROACTIVE MOLECULES TO THE CNS
AUTHOR: TAN S A (Reprint); AEBISCHER P
CORPORATE SOURCE: UNIV LAUSANNE, CHU VAUDOIS, SCH MED, GENE THERAPY CTR, CH-1011 LAUSANNE, SWITZERLAND (Reprint); UNIV LAUSANNE, CHU VAUDOIS, SCH MED, DIV SURG RES, CH-1011 LAUSANNE, SWITZERLAND
COUNTRY OF AUTHOR: SWITZERLAND
SOURCE: CIBA FOUNDATION SYMPOSIA, (1996) Vol. 196, pp. 211-236. ISSN: 0300-5208.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 113
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB At present, the aetiologies of many neurological and neurodegenerative diseases are unknown. However, emergence of a better understanding of these diseases, at both cellular and molecular levels, opens up the possibility of replacement **therapies**. The presence of the blood-brain barrier complicates the delivery of molecules to the central **nervous system**. Numerous attempts have been made to bypass this barrier either by delivering the drugs directly into the brain or by transplanting cells to produce the missing molecules in situ. This **review** explores several methods for delivering bioactive molecules into the CNS, including the use of permeabilizers, osmotic pumps, slow polymer release systems and transplantation of cells with or without the use of the encapsulation technology.

L9 ANSWER 24 OF 33 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 95:618944 SCISEARCH

THE GENUINE ARTICLE: RU150
TITLE: [redacted]ATE ON CELLULAR TRANSPLANTATION [redacted]NTO THE CNS AS A NOVEL **THERAPY** FOR CHRONIC PAIN

AUTHOR: CZECH K A (Reprint); SAGEN J
CORPORATE SOURCE: UNIV ILLINOIS, DEPT ANAT & CELL BIOL, 808 S WOOD ST, CHICAGO, IL, 60612 (Reprint)
COUNTRY OF AUTHOR: USA
SOURCE: PROGRESS IN NEUROBIOLOGY, (AUG 1995) Vol. 46, No. 5, pp. 507-529.
ISSN: 0301-0082.
DOCUMENT TYPE: General Review; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 119

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The transplantation of cells that secrete neuroactive substances with analgesic properties into the CNS is a novel method that **challenges** current approaches in treating chronic pain. This **review** covers pre-clinical and clinical studies from both allogeneic and xenogeneic sources. One cell source that has been utilized successfully is the adrenal chromaffin cell, since such cells constitutively release catecholamines, opioid peptides, and neurotrophic factors; release can be augmented with nicotine. Other **graft** sources include AtT-20 and B-16 cell lines which release enkephalins and catecholamines, respectively. For grafting in rodents, adrenal medullary tissue pieces are transplanted to the subarachnoid space. Chromaffin cell **transplants** can decrease pain sensitivity in normal rats using standard acute pain tests (paw-pinch, hot-plate, and tail-flick). In addition, **transplants** can restore normal pain thresholds in rodent models of chronic pain (formalin, adjuvant-induced arthritis, and sciatic-nerve tie) which closely similate the pathologies of human chronic pain conditions. Xenografts have been studied due to concerns that future application for human pain may be limited by donor availability. Despite immune Privileges of the CNS, xenografts require at least short-term immunosuppression to obtain a viable **graft**. Cell encapsulation is one method of sustaining a xenograft (in rat and human hosts) while circumventing the need for immunosuppression. Clinical studies have been initiated for terminal cancer patients with promising results as assessed by markedly reduced narcotic intake, visual analog scale ratings, and increased CSF levels of catecholamines and met-enkephalin.

L17 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:246746 BIOSIS
DOCUMENT NUMBER: PREV200100246746
TITLE: **Gene therapy** for diabetes.
AUTHOR(S): Demeterco, Carla (1); Levine, Fred (1)
CORPORATE SOURCE: (1) UCSD Cancer Center, La Jolla, CA, 92093-0912 USA
SOURCE: Frontiers in Bioscience, (Feb. 1, 2001) Vol. 6, No. Cited April 17, 2001, pp. d175-191.
http://www.bioscience.org/200
1/v6/d/demeter/fulltext.htm cited April 23, 2001
http://www.bioscience.org/. online.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English
AB For more than eighty years, insulin injection has been the only **treatment** option for all type I and many type II diabetic individuals. Whole pancreas transplantation has been a successful approach for some patients, but is a **difficult** and **complex** operation. Recently, it was demonstrated that a glucocorticoid-free immunosuppressive regimen led to remarkably successful islet transplantation. However, both pancreas and islet cell transplantation are limited by the tremendous shortage of cadaveric pancreases that are available for transplantation. Therefore, a major goal of diabetes research is to generate an unlimited source of cells exhibiting glucose-responsive insulin secretion that can be used for transplantation, ideally without the need for systemic immunosuppression. The focus of this **review** is on how **gene therapy** can be used in beta **cell replacement** strategies. Gene transfer to beta cells as well as recent advances in beta cell growth and development will be discussed.

L17 ANSWER 2 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:108147 SCISEARCH
THE GENUINE ARTICLE: 395RD
TITLE: Transplantation and **gene therapy**: Combined approaches for repair of spinal cord injury
AUTHOR: Murray M (Reprint); Fischer T
CORPORATE SOURCE: Med Coll Penn & Hahnemann Univ, Dept Neurobiol & Anat, Philadelphia, PA 19129 USA
COUNTRY OF AUTHOR: USA
SOURCE: NEUROSCIENTIST, (FEB 2001) Vol. 7, No. 1, pp. 28-41. Publisher: SAGE PUBLICATIONS INC, 2455 TELLER RD, THOUSAND OAKS, CA 91320 USA.
ISSN: 1073-8584.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 70
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Motor and sensory functions are lost after spinal cord injury because neurons die or atrophy and axons fail to regenerate. Until fairly recently, it was believed that damaged neurons could not be replaced and injured axons could not regenerate, and, therefore, functions dependent on

injured neurons could not be recovered, We now know that damaged neurons can be rescued by providing therapeutic factors or replaced by grafting. In addition, the adult CNS contains a population of precursor cells with a potential to generate new neural cells, whose numbers and composition can be modified by extrinsic factors. The pioneering studies of Aguayo demonstrated that CNS axons could regenerate in the right environment. Subsequent studies have revealed the identity of some of the inhibitory molecules in myelin and scar tissue, and we now have a better understanding of how the CNS environment can be modified to become more permissive to regeneration. Axons that regenerate must find an appropriate target, but it may not be essential to reestablish the precise topography for some functions to be restored. There are now new and promising strategies for delivery of therapeutic genes to protect neurons and to stimulate regeneration. The ability to engineer cells by **gene therapy** combines the therapeutic values of cell transplantation and gene delivery. These remarkable developments from many disciplines have generated a new level of optimism in the search for a cure for CNS injury and in particular spinal cord injury. In this **review**, the authors summarize recent progress in these strategies and some of the **challenges** that remain in elucidating the most efficacious protocols for rescuing injured neurons, encouraging regeneration of their axons, and promoting recovery of function.

L17 ANSWER 3 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2001:120084 SCISEARCH
THE GENUINE ARTICLE: 397LP
TITLE: Adrenocortical cells immortalized by telomerase: Potential use for **ex vivo gene therapy**
AUTHOR: Hornsby P J (Reprint); Ozol K; Yang K Y
CORPORATE SOURCE: Baylor Coll Med, Huffington Ctr Aging, 1 Baylor Plaza M320, Houston, TX 77030 USA (Reprint); Baylor Coll Med, Huffington Ctr Aging, Houston, TX 77030 USA; Baylor Coll Med, Dept Mol & Cellular Biol, Houston, TX 77030 USA; Baylor Coll Med, Dept Neurosurg, Houston, TX 77030 USA; Baylor Coll Med, Ctr Cell & Gene Therapy, Houston, TX 77030 USA
COUNTRY OF AUTHOR: USA
SOURCE: JOURNAL OF ANTI-AGING MEDICINE, (WIN 2000) Vol. 3, No. 4, pp. 411-417.
Publisher: MARY ANN LIEBERT INC PUBL, 2 MADISON AVENUE, LARCHMONT, NY 10538 USA.
ISSN: 1094-5458.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 37

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Telomerization, the process of immortalization of normal cells by expression of telomerase reverse transcriptase (TERT), could be of great use in biomedicine if the process allows cells to retain their normal properties and does not promote neoplastic transformation. In this article, we **review** the data on the potential uses of telomerized cells in **ex vivo gene therapy**, and discuss the issue of the potential risks of the use of this technology. We present preliminary data on the transplantation of telomerized bovine adrenocortical cells in the rat brain. Like other cell types, adrenocortical cells may be engineered to secrete desirable gene products. Currently, **problems** of immune rejection limit the usefulness of this potential **therapy**. We discuss future improvements in this cell transplantation system that could address these questions.

Telomerization, by removing the senescence barrier to unlimited cell proliferation, will greatly aid the genetic modification of cells in order to solve the issue of immune rejection and other **problems**.

L17 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:659299 CAPLUS
DOCUMENT NUMBER: 133:358784
TITLE: **Gene therapy** of neurodegenerative and demyelinating diseases
AUTHOR(S): Tenenbaum, Liliane
CORPORATE SOURCE: Laboratory of Experimental Neurosurgery Institut de Recherche Interdisciplinaire en Biologie Humaine et Nucleaire Universite Libre de Bruxelles, Brussels, B-1070, Belg.
SOURCE: NATO Sci. Ser., Ser. A (2000), 323(Targeting of Drugs: Strategies for Gene Constructs and Delivery), 53-68
CODEN: NASAF2; ISSN: 1387-6686
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A **review** with 74 refs. Neurodegenerative diseases (NDD) such as Parkinson's disease (PD), Alzheimer disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) are characterized by neuronal cell death. Demyelinating diseases (DMD) such as multiple sclerosis (MS) or Charcot-Marie-Tooth (CMT) disease are characterized by degeneration of oligodendrocytes (the myelin-forming cells of the central **nervous system**) or Schwann cells (the myelin-forming cells of the peripheral **nervous system**). Current **therapies** only provide symptomatic amelioration and are not curative. Neuroscience research has led to the identification of genes involved in neuronal or myelin-forming cell differentiation, death and survival and in some cases in genetic forms of these diseases. Even when the initial cause of degeneration is unknown, **nervous system** recovery can be promoted by **cell replacement** or gene delivery. Candidate genes are those protecting or rescuing degenerating cells (involving antiapoptotic genes, genes coding for trophic factors, antioxidant enzymes, etc..) or coding for compensatory enzymes. Various animal models mimicking neurodegenerative or demyelinating diseases have been developed and consist in e.g. inducing specific cell death either by injection of toxins directly in the central **nervous system** or by systemic administration. When available, mutant or transgenic mice can also be used. Gene delivery includes direct in vivo delivery using recombinant viruses or DNA **complexed** with non viral vectors such as liposomes, polyethylene-imine, etc.. and **ex vivo** gene delivery using heterologous or allogenous genetically-modified cells transplanted in the damaged area. Examples covering various animal models and therapeutic strategies will be given, with the aim to illustrate specific advantages and disadvantages of viral and non-viral vectors in clin. relevant situations.
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L17 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:20171 CAPLUS
DOCUMENT NUMBER: 130:245945
TITLE: Neural stem cell lines for CNS repair

AUTHOR(S): Martinez-Serrano, Alberto; Snyder, Evan Y.
CORPORATE SOURCE: Center of Molecular Biology "[redacted]ero Ochoa,", Autonomous University of Madr[redacted]CSIC, Madrid, Spain
SOURCE: CNS Regener. (1999), 203-250. Editor(s): Tuszynski, Mark H.; Kordower, Jeffrey H. Academic: San Diego, Calif.
CODEN: 67CYA3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A **review** with 112 refs. The establishment and use of stable, engraftable, clonal, multipotent neural stem cell lines have recently added an exciting new dimension to strategies for **cell replacement** and gene transfer to the diseased mammalian CNS. These neural stem cell clones can serve as convenient, well-controlled models for the in vivo study of CNS development and regeneration; can constitute readily available, well-characterized, safe sources of **graft** material for the replacement of multiple types of degenerated neural cells; and can provide excellent vehicles for the transfer of genes encoding diffusible and non-diffusible factors directly to the CNS. By exploiting their basic biol. properties, these cells are be able to bypass restrictions imposed by the blood-brain barrier to deliver therapeutic gene products in a sustained, direct, and perhaps regulated fashion throughout the CNS (either because they intrinsically produce these substances or because they have been genetically engineered **ex vivo** to do so). Furthermore, although they may disseminate these gene products throughout the brain, they nevertheless restrict that distribution to only the CNS. In addn., they may replace dysfunctional neural cells in both a site-specific and more global manner (circumventing the concern that in many alternative gene transfer techniques "new" genetic information is supplied to "old" neural circuits, many of which may have degenerated). Neural stem cell clones may be used for neurodegenerative conditions that occur both during development and in the mature brain. In fact, they appear to be capable of altering their migration and differentiation in response to certain as yet unspecified signals elaborated during active neurodegeneration. Thus, these vehicles may overcome many of the limitations of viral and non-neural cellular vectors, as well as pharmacol. and genetic interventions. A growing body of evidence has, indeed, affirmed the efficacy of a neural stem cell-based strategy for the replacement of defective or absent genes and cells, and has suggested that re-population of the diseased or injured CNS with such cells may promote both anatomical and behavioral recovery in animal models of neurodegenerative conditions. These recent expts. with clones of rodent neural progenitor and stem cells are bringing us rapidly closer to the **challenge** of repairing the CNS in genuine clin. settings using similarly well-characterized, fully controlled, multifaceted cellular tools of human origin.

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L17 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:724899 CAPLUS
DOCUMENT NUMBER: 128:73182
TITLE: Immortalized neural progenitor cells for CNS gene

transfer and repair

AUTHOR(S): Martinez-Serrano, Alberto; Bjo[redacted]lund, Anders
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SOURCE: Trends Neurosci. (1997), 20(11), 530-538
CODEN: TNSCDR; ISSN: 0166-2236
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A **review** with 58 refs. Immortalized multipotent neural stem and progenitor cells have emerged as a highly convenient source of tissue for genetic manipulation and **ex vivo** gene transfer to the CNS. Recent studies show that these cells, which can be maintained and genetically transduced as cell lines in culture, can survive, integrate and differentiate into both neurons and glia after transplantation to the intact or damaged brain. Progenitors engineered to secrete trophic factors, or to produce neurotransmitter-related or metabolic enzymes can be made to repopulate diseased or injured brain areas, thus providing a new potential therapeutic tool for the blockade of neurodegenerative processes and reversal of behavioral deficits in aminal models of neurodegenerative diseases. With further tech. improvements, the use of immortalized neural progenitors may bring us closer to the **challenging** goal of targeted and effective CNS repair.